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(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM CORPORATION [US/US]; P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : MILOSOVICH, Susan, Marie [US/US]; 167 Westridge Place North, Phoenixville, PA 19460 (US). RANDALL, Cynthia, Shea [US/US]; 700 Shawmont Avenue, Philadelphia, PA 19128 (US). RENCHER, William, Franklin [US/US]; 1027 Valley Forge Road, Unit 61, Devon, PA 19333 (US). ROSSI, Thomas, Mark [US/US]; 1371 Viking Drive, Dowingtown, PA 19335 (US). GOMBATZ, Kerry, Joseph [US/US]; 606 Westbourne Road, West Chester, PA 19382 (US).

(74) Agents: KANAGY, James, M. et al.; SmithKline Beecham Corporation, Corporate Patents-U.S., UW2220, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

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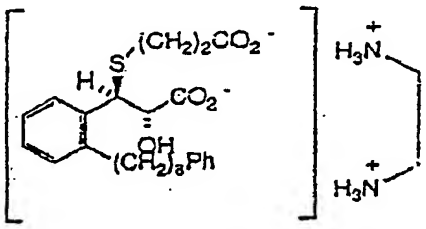

(I)

(57) Abstract

A polymorph of a monohydrate of an amine salt of a benzoic acid with formula (I) and aerosol formulations thereof are disclosed herein.

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AEROSOL FORMULATIONS

SCOPE OF THE INVENTION

This invention relates to an aerosol formulation comprising a triester of sorbitan and a salt of an LTD_4 antagonist analog of the peptido-leukotriene series, a substituted phenylcarboxy-alkylthioalkanoic acid. More particularly, this invention relates to an aerosol formulation made up of a long chain aliphatic triester of sorbitan and the 1,2-ethanediamine salt of [R-(R*,S*)]-β-[(2-carboxyethyl)thio]-α-hydroxy-2-(8-phenyloctyl)benzenepropanoic acid.

In a second aspect, this invention relates to the monohydrate form of the 1,2-ethanediamine salt (1:1) of [R-(R*,S*)]-β-[(2-carboxyethyl)thio]-α-hydroxy-2-(8-phenyloctyl)benzenepropanoic acid, a stable polymorph thereof and methods for making both.

BACKGROUND

Aerosol technology provides a convenient means for remotely dispensing and applying a host of different materials. These formulations are now a commonly used means for dispersing onto a surface any numbers of solid materials in a powder or liquid form. Aerosols are routinely used in the cosmetic industry, for painting, for dispensing insecticides and herbicides, for foaming materials, for applying cleaning and preservative agents and for administering drugs, to name a few of the various numerous applications of the aerosol technology.

Aerosols are quickly applied. Small amounts or a thin layer material can be rapidly applied over a large area in a repetitive fashion. Aerosol container are sealed. There is no back-aspiration during application so content contamination is greatly reduced in comparison with sprays or other forms of airborne application.

The word aerosol is classically defined as a collodial suspension of finely divided liquids or solid particles dispersed in and surrounded by a gas. An aerosol spray is obtained by forcing a mixture of gas and a liquid, semi-solid or solid material through a specially designed valve system resulting in a finely divided liquid or solid particles being dispersed in the gas stream.

Aerosol formulations have found use as a means for drug delivery and drug application. Pharmaceutical-based aerosol formulations are most frequently used orally or topically. Diseases

in the throat and lungs are frequently treated via aerosol formulations. Topical diseases such as acne or where there is need for first aid have utilized aerosol preparations. Anesthetics, antiseptics, germicides, body rubs, dermatological products and foot preparations are often applied via aerosols.

This invention is primarily concerned with the oral delivery of an anti-allergy agent. It is a particularly useful means for administering these drugs to prevent or treat asthma and other allergy-related or induced diseases of the mouth, throat or lungs.

Applicants have discovered that there are two unique phenomena associated with preparing an aerosol dispersion formulation of a certain asthma drug. First, a monohydrate of a polymorph is considerably more stable in the aerosol formulation. Secondly, applicants have discovered that the 1,2-ethanediamine salt of [R-(R*,S*)]-β-[(2-carboxyethyl)thio]-α-hydroxy-2-(8-phenyloctyl)-benzenepropanoic acid monohydrate is very sparingly soluble in triester sorbitans as compared with other dispersing agents which may be used in aerosol formulations.

Summary of the Invention

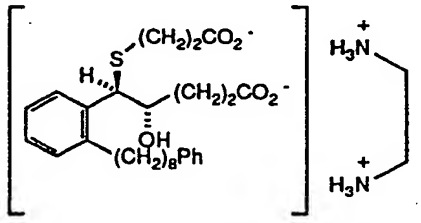
In one aspect this invention covers a pharmaceutically acceptable aerosol formulation comprising a sorbitan triester of C_{10} to C_{20} aliphatic acids, at least one propellant and the 1,2-ethanediamine salt of [R-(R*,S*)]-β-[(2-carboxyethyl)thio]-α-hydroxy-2-(8-phenyloctyl)benzenepropanoic acid monohydrate in an amount sufficient to deliver a therapeutically effective dose when inhaled.

Also, this invention covers a method for preparing a stable aerosol of the 1,2-ethanediamine salt of [R-(R*,S*)]-β-[(2-carboxyethyl)thio]-α-hydroxy-2-(8-phenyloctyl)benzenepropanoic acid monohydrate which comprises mixing the monohydrate with about a 10-fold excess of a sorbitan triester of C_{10} to C_{20} aliphatic acids and a propellant.

In a further aspect this invention relates to a monohydrate form of the 1,2-ethanediamine salt (1:1) of [R-(R*,S*)]-β-[(2-carboxyethyl)-thio]-α-hydroxy-2-(8-phenyloctyl)benzenepropanoic acid, a stable polymorph thereof and methods for making both.

SPECIFIC EMBODIMENTS

Pictorially, the acid salt of this invention is represented by the following formula.



The di-acid itself is disclosed in U.S. patent No. 4,820,719. That patent describes a synthetic process for making a racemic mixture of the acid and a means for recovering the isomer of this invention from that racemic mixture. Several salts of the acid, including the 1,2-ethanediamine salt, are also disclosed in that patent.

This compound is believed to be useful in treating asthma, especially when administered directly to the lung, a topical application for all intents and purposes. This indicated an aerosol formulation would be a useful means of administering this drug for treating asthma, as well as for other allergy-related diseases of the respiratory tract.

Monohydrate and Polymorph Formation

During the course of preparing formulations for various testing regimens, the anhydrous 1,2-ethanediamine salt material was used. It was not stable. It took up water, which in certain instances changed the characteristics of the formulations in which it was confected (for example, the aerosol formulation described herein). Research showed the 1,2-ethanediamine salt would form a monohydrate which then remained stable in various formulations, that is it did not take up more water or lose water as it was being formulated or during storage.

Further work with the monohydrate form of this 1,2-ethanediamine salt revealed changes were occurring in certain formulations during preparation or storage. Two polymorphs were isolated and characterized. One polymorph was found to be unstable. It converted to the other, more stable, form under certain conditions such as when sufficient heat was applied or certain formulating processes were carried out on the monohydrate.

Additionally, it has been found that certain solvent combinations used for making the monohydrate will give the desired polymorph directly, while others provide only the undesired (unstable) polymorph form. For example methanol- and ethanol-based solvent systems give the stable polymorph directly. Isopropanol/water and tetrahydrofuran/water mixtures may produce an unstable polymorph form of the monohydrate which must then be acted on further to convert it to the stable polymorph.

Solvents and solvent mixtures which produce satisfactory product, the stable polymorph of the monohydrate, are methanol, methanol containing up to 50% ethyl acetate, methanol/acetonitrile, and methanol/tetrahydrofuran, all containing about 1% water. The preferred solvent system is methanol or methanol/ethyl acetate/water, particularly this solvent in a 75:25:1 ratio. These figures are expressed in terms of volume/volume ratios.

One may vary the order of addition of reagents and the temperature of the reaction mixture during the formation of the salt. Reagents and substrates may be mixed together in any order at ambient temperature, and then heated to about 60°C. Alternatively, the substrate may be heated to 60°C in the chosen solvent system followed by the addition of reagents. Once precipitated, it is best to stir the reaction mixture for a period of time, preferably for about 3-16 hours, prior to filtering out the precipitate.

The stable polymorph can also be prepared by heating the unstable form to about 60°C, preferably in a solvent.

The stable polymorph of this invention is characterized by the differential scanning calorimetry (DSC) readout shown in Figure 1 and a crystal habit of thin blades or needles up to 100 microns long and 35 microns wide. By comparison, the unstable polymorph shows a crystal habit of rectangular plates approximately 350 microns by 250 microns. It is possible to distinguish between the two polymorphs based on powder X-ray diffraction; however, the differences are much more subtle than those exhibited by DSC.

The thermal behavior of the desired polymorph can be described and compared with the undesirable form thusly: The stable (desired) form exhibits a broad endotherm (onset about 100°C) followed by a large sharp endotherm (onset about 148°C) followed by a small sharp endotherm (onset about 165°C). This form corresponds

to the blade/needle form. The other polymorph (undesired form) is characterized by a large sharp skewed endotherm (onset about 130°C) followed by a moderate sharp endotherm (onset about 145°C) followed by a small sharp endotherm (onset about 165°C). This form corresponds to the plate form.

Aerosol Formulations

In early aerosol work, it was discovered that the formulations containing the anhydrous form of the 1,2-ethanediamine salt were physically unstable. By that it is meant that this anhydrous salt exhibited crystal growth in a sorbitan monoester-based aerosol formulation within a short period of time under accelerated storage conditions. Crystal growth of the type observed and the growth rate observed indicated such a formulation was essentially unusable because it would not have an adequate shelf life. Subsequently, a monohydrate was prepared and tested in the same formulation and under the same conditions. Surprisingly, the monohydrate showed substantially greater stability as compared with the anhydrous form.

Though this information was useful, an aerosol formulation still faced the problem of salt solubility in the suspending agent. A number of suspending agents were tested, oleyl alcohol, sorbitan monooleate, and oleic acid. The monohydride 1,2-ethanediamine salt was soluble in each of these to a degree which caused concern for product stability. It was projected that over time the fraction of solubilized monohydrate salt would recrystallize on existing monohydrate salt particles, thereby increasing the size of the monohydrate salt particles. This would not only affect the deposition pattern in the lung but could also impair the mechanical function of the valve. Then sorbitan trioleate was evaluated. It was found that the salt was very insoluble in this triester, especially as compared to the other suspending agents which had been tested. This salt was found to be about ten times less soluble in sorbitan trioleate as compared with the monooleate. Based on this novel finding, it was decided it was feasible to proceed with an aerosol formulation using a sorbitan triester, particularly a long chain fatty triester.

Sorbitan refers to the 1,4-sorbitan. It is made by dehydrating sorbitol. That process leaves three reactive hydroxyl groups one or more of which can be esterifed. In this case the triesters are formed by esterifying all three hydroxyl groups with a C_{10}-C_{20} acid.

Standard esterification processes are used to form these esters. Acids used to form these compounds may be fully saturated or have one or more double bonds. Preferably they will be mono-unsaturated or saturated. It is further preferred that each ester be formed using an acid of the same structure. However, it is expected that mixtures of acids and mixtures of esterified sorbitans could be used.

A number of these triesters are commercially available in the U.S. and worldwide. The most common triesters are sorbitan triisosterate and sorbitan trioleate. At least nine United States companies and three United Kingdom companies market these two sorbitan triesters under a host of different trade names. A listing of such companies and the products they produce is available in Pharmaceutical Excipients published by the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain, copyright 1986. Information on sorbitan triesters is also available from Remington's Pharmaceutical Sciences, the Merck Index and other compendia of pharmaceutical formulations.

The amount of drug used in the aerosol formulation will be based on the amount of material delivered each time the device is used. In this particular instance, it is most preferred to deliver between 100 µg of anhydrous free acid during each valve actuation. That means about 117 µg of the monohydrate 1,2-ethanediamine salt must be delivered each time. This represents what is believed to be an effective dose for treating asthma. But the therapeutically effective amount required to treat any given disease could vary between about 50 and 500 µg per dose depending on the disease, its response to this drug, how the aerosol container is used, and other factors affecting the effectiveness of the drug and the efficiency of delivery. Preferably the drug will be present in an amount between about 0.05 mg and 10.0 mg per gram of formula, most preferably about 2 mg per gram.

About 25 to 150 µl of aerosol should be delivered per actuation. This amount can be varied by modifying the valve design and by other means. But in any case, this volume should be such that it delivers a therapeutically effective amount of the drug.

The components from which aerosols are formed require a source of gas to act as the propellant and a solid, semi-solid or a

liquid which becomes dispersed in the gas as it is being dispensed through a valve system.

Aerosols can be classified as liquid-gas systems, compressed gas systems, and a third catch-all category which usually involves some type of piston or flexible bag device which assist in expelling the gas/solid dispersion through the valve system. A general discussion of the several aerosol systems routinely employed with pharmaceutical formulations can be found in Remington's Pharmaceutical Sciences, 17th edition, Mac Publishing Company, Easton, Pennsylvania, USA (1985).

One means of the mode of operation of aerosol systems is to use a liquified gas as the propellant source for forming the aerosol. This method introduces a liquified gas into a container. There an equilibrium is set up between a gaseous and liquid phase. The gaseous phase or vapor phase exerts a pressure on the system which is sufficient to dispel any portion of the liquified gas, it also contains the active ingredient, through a specially designed nozzle which forms the aerosol spray.

Liquified gas systems usually are two phase systems. A solution or suspension of an active ingredient is combined with a liquified gas and introduced into a sealed container with the appropriate aerosol valve system. As the name implies, a two-phase system once formulated in a can contains only a gas and a liquid propellant. The active ingredient can either be miscible, in solution, or immiscible, solid particles.

Compressed gas aerosol systems utilize an inert gas such as nitrogen, carbon dioxide or nitrous oxide, for example. Compressed gas is placed in a container and expands through the valve when the valve is opened providing the means for dispensing or expelling the container contents.

Valve structures and container forms and structures are known in the art. Remington's Pharmaceutical Sciences 17th Ed. illustrates a number of oral devices. Specialized aerosol applicators have been developed for oral administration of medicaments. These devices take into consideration the anatomical and physiological parameters and structure of the respiratory pathway. Most devices deliver an accurately metered dose of material in order to control the amount of medicament which is administered per use.

The propellants used in this invention may be liquified gases or compressed gases. Liquified gases are preferred. This class is made up of the halocarbons and hydrocarbons. Halocarbons have found greater use as they are inflammable as contrasted with hydrocarbons. Halocarbons are normally chloro or fluoro-substituted alkanes, most often of one or two carbons.

Fluorochlorocarbons are identified by two or three digit numbers which represent the number of fluoro, chloro, and hydrogen atoms in a particular propellant. The simplest of these fluorochlorocarbons, and two gases which can be used in the practice of this invention, are P_{11} and P_{12}. P_{11} is trichlorofluoromethane. P_{12} is dichlorodifluoromethane. Mixtures of these simple fluorochlorocarbons, that is the methane forms, are useful in the practice of this invention. But other combinations of these methane-based gases as well as other fluorochlorocarbons can be used.

Hydrocarbon gases are now also successfully used in pharmaceutical aerosols. Propanes, butanes and pentanes are frequently used in pharmaceutical aerosols. Dimethyl ether is also useful as a propellant in certain formulations, particularly because of its high water solubility as compared with the alkane-based propellants.

Compressed gases have at times been used in pharmaceutical formulations. However, depending on the nature of the formulation and the valve design, the dispensed product may be a mist, foam or semisolid. Only the mist form will be of real utility in this invention.

Liquified gas formulations are of most interest in this invention. Bulk concentrates are prepared by dispersing a known quantity of the 1,2-ethanediamine salt in a known quantity of a sorbitan triester/trichlorofluoromethane mixture by homogenization. This process should be carried out below room temperature (5-8°C). Preferably, it will be carried out under sterile conditions. Thereafter this dispersion is filled into an appropriate container for administering an aerosol orally. The system is pressurized with a propellant in a such a manner as to provide the desired amount for metering at a particular dose size per use.

Because the 1,2-ethanediamine salt is to be delivered to the lungs, these aerosols will be delivered via an inhaler of some sort adapted to use by mouth. A number of these devices have been

developed and are in use with different drugs. Several devices are illustrated in Remington's Pharmaceutical Sciences. These devices are readily available from a number of manufacturers or can be made by reference to published drawings and descriptions.

The following examples are set out to illustrate, but not limit, this invention. Reference is made to the claims for what has been reserved to the inventors.

Example 1

Preparation of the monohydrate of the 1,2-ethanediamine salt (1:1) of [R-(R*,S*)]-β-[(2-carboxyethyl)thio]-α-hydroxy-2-(8-phenyloctyl)-benzenepropanoic acid as the stable polymorph

This example illustrates how to make the salt, the monohydrate and the desired polymorphic form.

To a stirred solution of [R-(R*,S*)]-β-[(2-carboxyethyl)thio]-α-hydroxy-2-(8-phenyloctyl)benzenepropanoic acid (2.275 mol) in absolute methanol (10L) heated to 60°C, was added a solution of 1,2-ethanediamine (141.2g, 2.33 mol) in absolute methanol (2L) over a 30 minute period. After stirring at 60°C for 5 minutes, deionized water (120 mL) was added over a period of 0.5 minutes. After stirring this solution for 5 minutes, the solution was cooled slowly to approximately 50°C. When the internal temperature reached 45°C, the solution was seeded with 0.30 g of authentic monohydrate of the 1,2-ethanediamine salt (1:1) of [R-(R*,S*)]-β-[(2-carboxyethyl)thio]-α-hydroxy-2-(8-phenyloctyl)benzenepropanoic acid and then slowly cooled to ambient temperature over a period of 3 hours. After stirring at ambient temperature for approximately 16 hours, the mixture was filtered and washed two times with 1.5L of cold methanol containing 1% of deionized water. The product was air dried on the filter for 1 hour, then dried in vacuo (high vacuum) at ambient temperature until a constant weight was obtained (36 hours). The title product was obtained as a white powder.

^{1}H NMR (DMSO-d_6, 400MHz) δ 7.61 (br s, 1H), 7.27-7.23 (m, 2H), 7.17-7.13 (m, 3H), 7.05-7.02 (3H), 6.25 (br s, 6H), 4.46 (m, 1H), 4.02 (m, 1H), 2.83 (s, 4H), 2.65-2.59 (m, 1H), 2.56-2.46 (m, 5H), 2.38-2.21 (m, 2H), 1.53 (m, 4H), 1.29 (m, 8H); IR (KBr) 3512, 3014, 2926, 2853, 1557, 1403, 1097, 758 cm^{-1}

The polymorph made by this procedure produced a DSC of: a broad endotherm onset at 97.9°C (25.2 cal/g) followed by a sharp endotherm onset at 147.7°C (20.8 cal/g) and a small sharp endotherm onset at 163.1°C (1.6 cal/g). Mimima were recorded at 115.4°C, 150.0°C, and 164.4°C. This scan was generated on a 2.17 mg sample at a scan rate of 20.00 degrees per minute. (See Figure I)

This procedure can be carried out by stirring the solution with all ingredients for 3 hours instead of 16 and still achieve acceptable results.

The foregoing procedure was repeated using a methanol/ethyl acetate solvent system (75:25) containing 1% water. Equivalent results were obtained.

Example 2

Preparation of the Monohydrate

To a stirred solution of [R-(R*,S*)]-ß-[(2-carboxy- ethyl)thio]-α-hydroxy-2-(8-phenyloctyl)benzenepropanoic acid (2.275 mol) in absolute methanol (10 L) heated to 60°C, was added a solution of 1,2-ethanediamine (141.2 g, 2.33 mol) in absolute methanol (2 L) over a 30 minute period. After stirring at 60°C for 5 minutes, deionized water (120 mL) was added over a period of 0.5 minutes. After stirring at 60°C for 5 minutes, the reaction solution was cooled slowly to approximately 50°C. When the internal temperature reached 45°C, the solution was seeded with 0.30 g of authentic title compound and then slowly cooled to ambient temperature over a period of 3 hours. After stirring at ambient temperature for approximately 16 hours, the product was isolated by filtration and washed two times with 1.5 L of methanol containing 1% of deionized water. The product was air dried in the filter for 1 hour, then dried *in vacuo* (hi-vacuum) at ambient temperature for 36 hours to a constant weight. This afforded [R-(R*,S*)]-ß-[(2-carboxyethyl)thio]-a-hydroxy-2-(8-phenyloctyl)benzenepropanoic acid, 1,2-ethanediamine (1:1), monohydrate as a white powder. The particle size was reduced by fluid energy grinding in a stainless steel mill to afford the title compound as a fine white powder: ^{1}H NMR (DMSO-d_6, 400 MHz) w 7.61 (br s, 1H), 7.27-7.23 (m, 2H), 7.17-7.13 (m, 3H), 7.05-7.02 (3H), 6.25 (br s, 6H), 4.46 (m, 1H), 4.02 (m, 1H), 2.83 (s, 4H), 2.65-2.59 (m, 1H), 2.56-2.46 (m, 5H), 2.38-2.21 (m, 2H), 1.53 (m,

4H), 1.29 (m, 8H); IR (KBr) 3512, 3014, 2926, 2853, 1557, 1403, 1097, 758 cm^{-1}.

Example 3

Salt Solubility

The anhydrous form of the entylenediamine salt, when formulated with sorbitan trioleate, demonstrated crystal growth after two weeks at 50°C and 40°C at 75% relative humidity

The monohydrate form of the 1,2-ethanediamine salt, when formulated with sorbitan trioleate, did not demonstrated crystal growth after six months storage at 30°C and three months storage at 50°C and 40°C at 75% relative humidity.

Example 4

Testing of the monohydrate in Sorbitans

The solubility of the 1,2-ethanediamine salt of [R-(R*,S*)]-β-[(2-carboxyethyl)thio]-α-hydroxy-2-(8-phenyloctyl)benzene-propanoic acid monohydrate in sorbitan mono-oleate and sorbitan trioleate was determined. Sorbitan trioleate was determined by HPLC analysis. The following results were obtained:

Sorbitan trioleate	0.6 µg/ml
Sorbitan mono-oleate	6.2 µg/ml.

As crystal growth is a function of solubility the trioleate was deemed to be a superior suspending agent for use in making an aerosol formulation of this salt.

Example 5

Aerosol Formulation

An aerosol formulation was prepared by mixing the following ingredients and amounts.

Ingredient	Amount
Drug	36.0 mg
Sorbitan Trioleate	3.6 mg
Trichlorofluoromethane	5.4 g
Dichlorodifluoromethane	12.6 g

Eighteen grams of this mixture were filled into 19 ml, anodized aluminum "cut-edge", 20 mm neck, aerosol canisters (Presspart C128) crimped with 50 µl metering valve (Bespak BK356). The rubber components of the valve had been pre-extracted by the manufacturer utilizing a total immersion method. An alternative valve system M3652, produced by 3M Health Care Specialities valve of Saint Paul, Minnesota, USA.

What is claimed is:

1. A composition of matter which is the monohydrate of the 1,2-ethanediamine salt (1:1) of [R-(R*,S*)]-β-[(2-carboxyethyl)thio]-α-hydroxy-2-(8-phenyloctyl)benzenepropanoic acid.

2. A stable polymorph of the compound of claim 1 which shows a DSC scan having the following characteristics: a large broad endotherm (onset about 100°C) followed by a large sharp endotherm (onset about 148°C) followed by a small sharp endotherm (onset about 165°C).

3. A process for making the stable polymorph of claim 2, which process comprises combining 1,2-ethanediamine and [R-(R*,S*)]-β-[(2-carboxyethyl)thio]-α-hydroxy-2-(8-phenyloctyl)benzene-propanoic acid in a methanolic solution with about 1% water at a temperature between about 20°C to the boiling point of the solvent, then recovering the resulting monohydrate as the stable polymorph.

4. The process of claim 3 wherein only methanol is used.

5. The process of claim 4 wherein ethyl acetate, acetonitrile or tetrahydrofuran is used as a co-solvent.

6. The process of claim 5 where the methanol/ethyl acetate ratio is 75:25.

7. The process of claim 3 where the solution is heated to about 60°C.

8. An pharmaceutically acceptable aerosol formulation comprising a sorbitan triester of C_{10} to C_{20} aliphatic acids, at least one propellant and the 1,2-ethanediamine salt of [R-(R*,S*)]-β-[(2-carboxyethyl)thio]-α-hydroxy-2-(8-phenyloctyl)benzenepropanoic acid monohydrate in an amount sufficient to deliver a therapeutically effective dose when inhaled.

9. An aerosol according to claim 8 where the propellant is a halocarbon.

10. An aerosol according to claim 9 where the triester is the trioleate.

11. An aerosol according to claim 10 where the salt is present in a concentration of between about 0.00005 and 0.01 g per gram of aerosol.

12. A method for preparing a stable aerosol of the 1,2-ethanediamine salt of [R-(R*,S*)]-β-[(2-carboxyethyl)thio]-α-

hydroxy-2-(8-phenyloctyl)benzenepropanoic acid which comprises mixing the monohydrate with about a 10-fold less amount by weight of a sorbitan triester of C_{10} to C_{20} aliphatic acids and a propellant.

13. The method of claim 12 where the triester is the trioleate.

14. The method of claim 14 where the salt is present in an amount of between 0.00005 and 0.01 grams per gram of aerosol.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/02177

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07C323/56; A61K31/205; C07C319/26; A61K9/12

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07C

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	US,A,4 820 719 (GLEASON ET AL) 11 April 1989 cited in the application see claim 7; examples 35-36	1

* Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
20 JANUARY 1992	25 02. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	J. VAN GEYT

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9102177 SA 52062

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 20/01/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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